The Clinical Pathology of Syphilis of the Eye.

BY

SYDNEY STEPHENSON, D.O.Oxon.

A Clinical Lecture given on June 19th, 1914, to the candidates for the Diploma in Ophthalmology of the University of Oxford.

Reprinted from THE MEDICAL PRESS AND CIRCULAR
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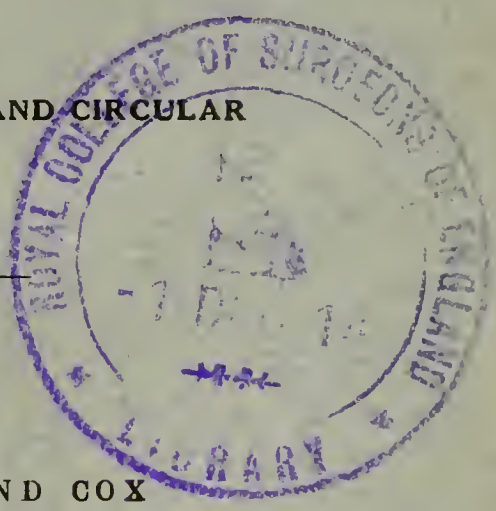

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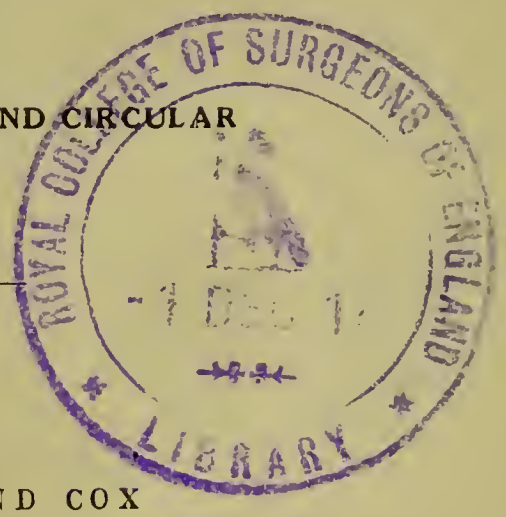

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THE CLINICAL PATHOLOGY OF SYPHILIS OF THE EYE.

GENTLEMEN,—It would be the veriest truism to say that syphilis, inherited or acquired, is a common cause of disease of the eye. That much is known to everybody. But to-day the position in regard to syphilis has undergone a remarkable development by reason of four relatively recent advances, in which ophthalmology is not less concerned than other branches of medicine. They are as follows :

1. The discovery by Metchnikoff and Roux in 1903 that syphilis could be inoculated into the preputial fold of the clitoris or the eyebrow of the chimpanzee (*Troglodytes niger* and *calvus*) with the production of a chancre and of secondary symptoms, and could be transmitted from one chimpanzee to another.

2. The recognition by Schaudinn and Hoffmann in 1905 of the protozoon or bacterium known as the *Spirochæta pallida* or *Treponema pallidum* as the cause of the disease.

3. The sero-diagnosis of syphilis, introduced by August von Wassermann in 1906, which allows us to recognise the existence of the disease in a patient's system and to check the results of treatment, altogether apart from clinical manifestations.

4. The discovery by Ehrlich and Hata in 1909 of an arsenical compound, "salvarsan," which, when injected into the veins, usually has a striking and rapid effect upon the clinical manifestations of syphilis. In this connection the still more recent discovery by Ehrlich of "neosalvarsan," a formaldehyde compound of salvarsan, must also be mentioned.

The *Spirochæta pallida* has now been found in all kinds of syphilitic lesion and in all stages of the malady. In primary and secondary lesions,

particularly in chancres, condylomata, and enlarged lymphatic glands, its demonstration is easy, always provided specific treatment has not been employed. On the other hand the *Spirochæta pallida* can be found with difficulty and only in small numbers in gummatous lesions, thereby supporting the view long held on clinical grounds—namely, that the infectivity of tertiary manifestations, if it existed at all, was extremely slight.

It is important to recall the fact that H. Noguchi has now succeeded in cultivating the organism of syphilis. For this purpose he employs serum-water, to which is added a piece of rabbit's tissue—such as sterile kidney or testicle. The culture fluid is inoculated with morsels of the syphilitic testis of an infected rabbit. The medium is incubated anaërobically by the simple expedient of covering the surface with a layer of sterile paraffin. The cultivated spirochætes produce, when implanted into the testis of a rabbit, characteristic histological changes, and the *Spirochæta pallida* grows and multiplies. There is no reason whatever for thinking that man would prove immune to the infection.

It will thus be seen that the *Spirochæta pallida* fulfils all Koch's postulates, and it does not now admit of the least doubt that it is the actual cause of syphilis.

The virus is destroyed by filtration, as well as by exposure to X-rays or to a temperature of 48° C. for half an hour.

The *Spirochæta pallida* has been found in several specific lesions of the eye. For example, it has been demonstrated in primary sclerosis of the eyelids and conjunctiva (Aubineau, Chaillous, Cauvin, Chevallereau), in the conjunctival muco-pus from a child with congenital syphilis (Duperié), in a mucous patch of the conjunctiva (McKee), in the corneæ of infants suffering from keratomalacia (Stephenson, v. Hippel), in the aqueous humour withdrawn from cases of acute irido-cyclitis (zur Nedden, Puccioni, Stephenson), and, lastly, in the cornea of cases of interstitial keratitis (Igersheimer, Clausen).

Syphilis has for long been classed among the so-called "infective granulomata," and its histological lesions accordingly fall into line with those which characterise that group as a whole. Histological diagnosis, indeed, is often impossible. After very careful examination of a specimen, the most that one may be in a position to say is that the lesion belongs to one of the chronic infective granulomata (P. N. Panton[1]). Moreover, it is rare to get opportunities for removing syphilitic tissue from the eye during life, so that the material for histological examination is by no means easy to come at.

The primary lesion, the Hunterian chancre, when it occurs on the conjunctiva or skin of the eyelids does not differ pathologically from a sclerosis in the more usual site. It is made up of round and endothelial cells, intermingled with which giant-cells may sometimes be found. In the later stages plasma cells and fibroblasts make their appearance. The vessels of the part show the changes of endarteritis and periarteritis. Spirochætes invade the walls of the blood-vessels, but occur chiefly in aggregations around the latter. Most of the granuloma is eventually removed by ulceration, or it undergoes fibrosis and never becomes a "sore" in the ordinary sense and acceptation of that word.

The lesions of the secondary stage, broadly speaking, consist of round-celled tissue containing the *Spirochæta pallida*, and the resulting granuloma sooner or later undergoes absorption, organisation, or destruction.

From a histological standpoint, the gumma of the tertiary stage is one of the most characteristic of syphilitic products. At the onset it is made up of granulation tissue. But in the course of growth one or more caseous foci are formed towards the central parts of the gumma, and the parts immediately surrounding these degenerate foci become converted into cicatricial tissue. In brief, then, the leading changes comprise caseation and fibrosis.

A typical gumma has three zones:—(1) a caseous centre, (2) a zone of surrounding cicatricial tissue, and (3) a zone of granulation tissue in which giant-cells are by no means infrequent. Side by side with the foregoing changes the blood-vessels

show the changes collectively known as "vasculitis" —that is to say, proliferation of the endothelium, together with infiltration of all three coats with small round cells. Later, the vessel wall becomes narrowed, distorted (*endarteritis deformans*), or even occluded (*endarteritis obliterans*) by the irregular thickening of the intima. The necrosis of gummata, which furnishes us with one of their most characteristic clinical features, is largely due to this syphilitic endarteritis.

Endarteritis, indeed, may be said to dominate the histo-pathology of all stages of syphilis. Already in the Hunterian sore, doubtless owing to the lodgment and multiplication of the spirochætes, peri- and endarteritis are present. In the skin lesions of the secondary stage, again, the small vessels of the part show signs of endarteritis and evidence of an exudation of small cells around their walls. In specimens from the iritis of secondary syphilis, too, the small vessels of the iris manifest endarteritis and thickening of the adventitia, while the stroma is infiltrated with small round cells. That, after all, is no more than might be expected when we recollect that the spirochætes and their toxins invade the system from the primary sore by spreading along the walls of the blood- and lymph-vessels. Their embolic lodgment at a suitable site is followed by cellular infiltration, which represents the reaction of the tissues to the irritant, and probably by more or less structural damage to the part.

From the foregoing sketch it follows, then, that there is a considerable likeness between the histological changes of tubercle, on the one hand, and those of syphilis, on the other, although endarteritis is commoner in the latter than the former. The points that would suggest a syphilitic lesion include caseation, fibrosis, proliferation of the interior of the arterioles, and a cellular infiltration with lymphoid and plasma cells (P. N. Panton). At the same time in cases of doubt as between the two we must appeal to the presence or absence of the *B. tuberculosis* or the *S. pallida* respectively.

The histo-pathology of one outstanding syphilitic affection of the eye—namely, interstitial keratitis, is now tolerably well understood, owing to the fact

that it can be produced experimentally in some of the lower animals. This endogenous inflammation, as well known, may occur either in inherited or acquired syphilis, although it is much commoner and more obstinate in the former than the latter. It has been assigned to some dyscrasic factor of a toxic nature (Panas), but that view is now fast losing ground, since an identical affection has been induced in rabbits (Bertarelli, Scherber, v. Benedek) and in apes (Greeff, Clausen, Schucht) by inoculation of the eye with human syphilitic products, such as chancres and condylomata. Under these circumstances, moreover, the *Spirochæta pallida* has been demonstrated in the tissues of the affected corneæ by Bertarelli, Greeff, Clausen, and Schucht.

The dyscrasic theory can be shown to be improbable on other grounds, particularly in the light of the experimental production of a species of interstitial keratitis by injection to the blood stream or anterior chamber of the eye of the *Trypanosoma gambiense*, a first-cousin of the *S. pallida*. The trypanosome has been found on section of the inflamed cornea by Stargardt, Morax, Yorke, and others.

To the view that interstitial keratitis may result from toxins produced by the spirochætes elsewhere in the body, the death blow appears to have been given by recent experiments by K. Stargardt(2). That surgeon found that blood containing trypanosomes injected into the limbus, aqueous, or vitreous of rabbits or guinea-pigs gave rise in many instances to interstitial keratitis, and a similar result followed the injection of pure trypanosomes. On the contrary, no inflammation of the cornea followed the injection of the toxins of trypanosomes or the dead trypanosomes themselves.

That the *Spirochæta pallida* can be found in the unaffected corneæ of syphilitic fœtuses and babies, as well as in some other parts of the eye, has been shown by Peters, Gierke and Stock, Bab, Schlimpert, and myself. The organisms, or their "granules," appear to remain latent and to produce no symptoms, probably aided and abetted by the peculiar circulatory conditions of the cornea. Then, in response to some factor or factors, of

which we know positively that traumatism is one, they become active and multiply, and clinically an interstitial keratitis is the result.

The histological changes found in interstitial keratitis, whether of idiopathic or experimental production, are essentially of a gummatous character, and it is probable that the more severe cases are accompanied by similar alterations in the anterior parts of the uveal tract. The salient feature, when examined under the microscope, is an infiltration of the deeper layers of the cornea with round cells, and along with them giant and endothelioid cells may occur. In this way quite large cellular accumulations may separate the lamellæ of the cornea. The central parts of the gummatous nodules may undergo caseation. Other changes include œdema of the corneal epithelium and of the tissues of the cornea, and extension of vessels into the substantia propria from the surrounding vascular tissues. The corneal process often resolves to a greater or less extent, but it may on occasion break down into an ulcer or give rise to a bleb, or produce changes in the curvature of the cornea or even give rise to a staphyloma.

Since Bertarelli produced experimental keratitis by inoculating the corneæ of rabbits with syphilitic products, it has been known that the corneal lesions contained an abundance of spirochætes. Inoculations carried out in the dog by Hoffmann and Bruning, and in the cat by Levaditi and Yamanouchi, have yielded similar results. More important still, as the result of recent work it has been shown that the *Spirochæta pallida* is actually present in human corneæ affected with interstitial inflammation, as some of us had surmised. For example, Igersheimer (3) excised a patch of the diseased tissue from the eye of a lad, æt 14, and demonstrated the spirochætes in sections. The wound was covered with conjunctiva, and the eye did well. Again, at a meeting of the Berlin Ophthalmological Society held on November 24th, 1910, Clausen(4) exhibited specimens, stained by the Levaditi method, obtained from the eye of a boy suffering from interstitial keratitis. Spirochætes were present.

Very suggestive were the experiments carried

out in 1912 by J. Igersheimer(5). He produced inflammations of the eye by injecting cultures of the *Spirochæta pallida* into the carotid artery of rabbits. The day after the operation, grey or whitish foci of choroiditis could be detected in the fundus oculi. In some instances there was injection of the ciliary or conjunctival vessels, opacities of the cornea, and exudation or hæmorrhages into the anterior chamber. The remote results included ulceration of the lid (with spirochætes), parenchymatous keratitis, iritis, and atrophy of the optic nerve. In short, Igersheimer claims to have succeeded in setting up conditions in the rabbit's eye in every way comparable with those of human syphilis by injecting pure cultures of the *Spirochæta pallida* into the arterial circulation of the head.

The Pathological Diagnosis of Syphilis of the Eye.

In external lesions of the eye, such as suspected chancres or condylomata or mucous patches of the skin or conjunctiva, an attempt should always be made to clench the diagnosis by demonstrating the *Spirochæta pallida*. This is not a very difficult task, provided neither general nor local treatment has been employed. It is one that lies well within the compass of any scientific ophthalmic surgeon. The syphilitic nature of any given lesion should never be negatived until repeated examinations have failed to disclose the presence of the *Spirochæta pallida*, and perhaps not even then.

The organism of syphilis, as is well known, stains with considerable difficulty. The best re-agent to employ for this purpose is Giemsa's famous fluid, whereby the *Spirochæta pallida* is usually stained pink and other spirochætes and organisms blue. It averages about 12 μ in length (a red blood corpuscle measures about 7.5 μ in diameter), its ends taper, and it is made up of from 8 to 20 corkscrew-like spirals. It is important to recall the fact that the *Spirochæta pallida*, almost alone among the spirochætes, retains its spiral arrangement not only during movement but also when at rest. In other words, its spirals represent a permanent

arrangement. The only other spirillum possessing a fixed spiral disposition is the *Spirochæta dentium*, a common inhabitant of the mouth. That organism stains with the ordinary stains, and its length is only about one-half that of the *Spirochæta pallida*.

The *technique* of collecting material for the demonstration of the *Spirochæta pallida* may be described at follows:—The sore or other external lesion is first cleansed with bits of wool damped with saline, and is then squeezed with the fingers or scraped lightly with a blunt instrument. The serous fluid thereby obtained is smeared lightly upon the surface of several cover-slips. An even better plan is that recommended by Phillips and Glynn. The lesion is cleansed with cotton wool, and then wiped over with wool previously soaked in methylated spirit. After a few moments, the alcohol is wiped away, and the clear serum which soon exudes is taken for the purposes of the examination.

In order to find the spirochætes, several plans are in vogue, as follows:—

(*a*) Giemsa's Stain.—The preparation, obtained as described above, is fixed by gentle heat, and is then stained with azur II-eosin. Ten drops of the stain are gently mixed with 10 c.c. of tap water, and in accordance with the plan recommended by McDonagh(6), the smear is covered with the mixture, and heated over the flame until vapour rises. It is then left for thirty seconds, when the fluid is poured away. Fresh stain is poured on to the specimen, which is again heated. The process is repeated four times all told. Finally, the specimen is washed in tap water, dried, and mounted.

There are other methods of staining smear preparations of the *Spirochæta pallida*, as Marino's and Leishman's, but we need scarcely discuss these in this brief sketch.

(*b*) Burri's Method.—The secretion from the suspect lesion is placed upon a slide and mixed, while still moist, with an equal quantity of liquid Chinese ink. From the mixture cover-films are prepared, and examined with the oil immersion lens. The unstained spirochætes stand out very distinctly against the dark background produced by the ink. By the way, a special ink, known as Günther-

Wagner's, is used in the process. It is for all practical purposes homogeneous, and all contained micro-organisms have been destroyed by steaming.

(*c*) Dark Ground Illumination.—By most writers the method of dark ground illumination is now regarded as the best for the discovery of the *Spirochæta pallida*, since the movements of the protozoon can be watched, and there is distortion neither in form nor size. The method requires some additions to the ordinary bacteriological microscope, including a dark ground condenser, a stop, and a Nernst lamp, the total cost of which need not exceed three pounds.

As regards the deeper lesions of the eye, as those of the uveal tract, we must in the ordinary course of events trust to sero-diagnosis or to certain other specific biological tests.

This is hardly the place to discuss the principles which underly the Wassermann reaction, let alone the *technique* of the process. Those are described in every book on pathology. It is of more importance for us to endeavour to obtain some sound notions as to the range of usefulness of the reaction in the everyday practice of ophthalmology.

Four axioms concerning the Wassermann reaction will be generally conceded nowadays :—

1. That the reaction, when obtained, is proof positive of a syphilitic infection. (*a*)

2. That a negative Wassermann does not, and never can, enable us to aver that syphilis is absent.

3. That a positive reaction, even in the absence of clinical symptoms, is enough of itself to justify the employment of spirillicidal remedies, as salvarsan or mercury.

4. That the *technique* originally employed by Wassermann is more trustworthy than any of its subsequent modifications.

It is of interest to enquire in what proportion of cases of syphilis we may expect to find the Wassermann reaction positive. H. W. Bayly(7) determined the point in upwards of 500 untreated or but slightly

(*a*) The non-specific diseases that are known to yield a high percentage of positive results include Yaws, Leprosy (tuberculous form), Malaria, and Trypanosomiasis. Positive results of a transient nature have also been reported in pneumonia and scarlet fever.

treated cases, and obtained a positive reaction in 85 per cent. According to figures, collated from British, American, German, and Swedish sources by the same author, in congenital syphilis the percentage has ranged from 88 to 95; in primary syphilis from 38 to 90; in secondary syphilis from 79 to 92; and, lastly, in tertiary syphilis from 63 to 100.

As regards particular diseases of the eye, the figures recently published by Mouradian[8] of Paris may be quoted:—Iritis and irido-cyclitis, 39 per cent.; oculo-motor paralyses, 50 per cent.; interstitial keratitis, 66 per cent.; chorio-retinitis, 24 per cent.; scleritis, 33 per cent.; and optic atrophy 25 per cent. By adding his own figures to those given by other observers, Mouradian has arrived at the following totals:—Choroiditis and retinitis, 18 per cent.; optic neuritis, 19 per cent.; iritis and irido-cyclitis, 29.4 per cent.; scleritis, etc., 33.3 per cent.; optic atrophy, 37.9 per cent.; ocular paralyses, 42.1 per cent.; ocular tabes, 76.4 per cent.; and interstitial keratitis, 84.5 per cent.

A positive reaction forms an unconditional indication for specific treatment, since it implies that active spirochætes are present, no matter how remote the original infection. At the same time, as insisted upon by almost every writer on the subject, it does not tell us whether this or that eye disease is of specific origin. It merely indicates that syphilis, manifest or latent, is present in the system. It goes almost without saying that there is nothing whatever to prevent an affection of the eye, say, of tuberculous origin, from occurring in a syphilitic subject. It has been surmised by G. Schumacher[9], indeed, that an eye which has been attacked by hereditary syphilis is particularly liable to a secondary tuberculous infection. This furnishes one among many other reasons why we must never neglect to examine the patient thoroughly from a clinical point of view.

Anti-syphilitic treatment is known to destroy the spirochætes, to release much endotoxin, to occasion an outburst of cellular degeneration, and, last, but not least, gradually to abrogate the Wassermann reaction. Hence the scanty value to be attached to a negative reaction in a patient who has been

treated with mercury, salvarsan, or neo-salvarsan. The point to bear in mind is, that a positive result in an individual not so treated is an unfailing proof of the presence of syphilis.

The control of treatment by the serum reaction is still somewhat of a vexed question. Neisser believes that recurrence is possible in all patients who yield a positive reaction. Such cases, therefore, should be placed under treatment. The length of the course should be determined by the presence or absence of the Wassermann reaction. W. d'Este Emery[10] has recently expressed the opinion that the non-reappearance of the reaction within a year of its removal by the use of spirillicidal agents denotes the cure of the malady. If a still further guarantee of cure be called for, it will be found in the administration of a so-called "provocative" dose of salvarsan. Then, if the reaction still remains negative, Emery believes that the chain of evidence is complete.

The matter is complicated by the fact that even after the injection of salvarsan or neo-salvarsan the reaction may remain positive for a long time. It is thought by McIntosh and Fildes[11] that under such circumstances the quantitative estimation should always be carried out. In favourable cases the reaction will then be found to become less and less strong, while in the contrary event more salvarsan must be given, or mercury be applied is some more efficacious way.

Attempts have been made to invoke the phenomena of anaphylaxis or allergy in the diagnosis of syphilis, much in the same way as they have already been utilised in the recognition of tubercle or glanders by von Pirquet's reaction and the mallein test respectively.

The *Spirochæta pallida* is believed to fulfil all the requirements that lead to the development of an anaphylactic state in syphilitic subjects. Until the recent work of Hideyo Noguchi, the difficulty was to obtain a trustworthy antigen (*i.e.*, a substance which, when injected, would produce an antibody), but now such an antigen is made from pure cultures of the *Spirochæta pallida*. The cultures in ascitic fluid and in ascitic fluid agar, to which sterile placenta has been added, after varying

periods of growth, are ground up and emulsified with fluid media. The preparation is next heated to 60° C., and, lastly, to ensure sterility, 0.5 per cent. of carbolic acid is added.

This product, to which Noguchi has given the name "Luetin," is injected into the skin of the arm. A positive result is shown after twenty-four hours by more or less inflammatory reaction at the site of the injection, and the symptoms increase during the next few days. In accordance with the type of reaction, Noguchi distinguishes three forms —namely, the "papular," the "pustular," and the "torpid." Slight constitutional symptoms, as manifested by rise in temperature, have been noted.

The luetin test is not likely to yield a positive result in secondary syphilis, and even less likely to do so in primary syphilis. In the former it is therefore less trustworthy than the Wassermann reaction, and in the latter than the discovery of spirochætes in the local lesion or in the glands connected therewith. But under some other circumstances it seems to possess considerable diagnostic value. Thus, in tertiary cases giving a negative Wassermann reaction, the luetin test often yields positive information. For example, M. Cohen (12) obtained a positive reaction in 10 eye cases regarded clinically as syphilitic, where the Wassermann reaction had proved negative. Confirmatory observations of the kind have recently been published by S. H. Browning(13). In 76.66 per cent. of Cohen's cases the results of the luetin test agreed with the clinical evidence, as well as with the results of the Wassermann reaction.

In short, there now appears to be every indication that the new test will prove itself of value in the type of case not infrequently met with in eye work—such as old choroido-retinitis, the syphilitic origin of which cannot usually be brought out by the Wassermann reaction, even if a provocative dose of salvarsan be first administered. The luetin test has one obvious advantage for the ophthalmic practitioner over the Wassermann reaction—namely, that its simplicity of *technique* allows it to be carried out by the surgeon himself. As Browning(13) remarks, the luetin test "brings within the

reach on all practitioners a simple and reliable test for syphilis, the result of which they can see and judge for themselves."

The latest test is known as the "Pallidin reaction," the *technique* of which has been described by E. Klausner(14). The organ extract, which is vaccinated into the patient's skin, is obtained from lungs affected with white pneumonia. It is stated to be a certain diagnostic test in tertiary or inherited syphilis, but, curiously enough, to be negative in tabes, general paralysis, and specific disease of the arteries.

Klausner(15) has employed the new method at Professor Elschnig's clinic at Prague in one hundred cases of eye disease, where syphilis was suspected. He obtained a positive result in 20 per cent., whereas the Wassermann reaction was positive in 16 per cent. The results of the two methods tallied closely in many instances, particularly in irido-cyclitis, cyclitis, iritis, papillitis, and retino-choroiditis. Differences were noted in retro-bulbar neuritis, ophthalmiaplegia externa, and scleritis, but, then, the number of cases was very small. In twenty cases of interstitial keratitis the Wassermann gave 33 per cent. and the Pallidin reaction 60 per cent. of positive reactions. Klausner's investigations lead him to regard the Pallidin reaction as a useful complement to the serum reaction.

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